cessing many specimens for the polymerase chain reaction has recently become available.

The speed and sensitivity of the reaction procedure offer advantages for both prenatal and microbiologic diagnosis. The method has been applied to the prenatal diagnosis of sickle cell anemia and will find wider application as the genetic defects underlying other familial disorders are identified. It is also capable of detecting minute quantities of viral DNA in clinical specimens even before seroconversion occurs. The polymerase chain reaction has already proved useful in research laboratories for detecting mutations of cellular proto-oncogenes that are thought to play a role in human carcinogenesis; it may soon be used clinically to characterize these mutations in individual patients.

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Fine-Needle Aspiration Biopsy in the Diagnosis of Lymphadenopathy in Persons at Risk for AIDS

LYMPHADENOPATHY is a common finding in the acquired immunodeficiency syndrome (AIDS) and in the AIDS-related complex (ARC). Although this lymphadenopathy usually has a restricted differential diagnosis, it can be difficult to establish the precise cause of the nodal enlargement by history, physical examination, radiographic studies, and laboratory tests.

At the San Francisco General Hospital and Medical Center, we have found fine-needle aspiration (FNA) biopsy to be an accurate, well-tolerated, cost-effective, and useful method to initially evaluate lymphadenopathy in patients with AIDS or ARC. We have done more than 120 FNA biopsies of lymph nodes in such patients.

In our experience, about half the lymph node biopsy specimens in such patients show lymphoid hyperplasia. The other half reveal non-Hodgkin's lymphoma, mycobacterial infection, Kaposi's sarcoma, Hodgkin's disease, and various metastatic tumors. The smears showing lymphoid hyperplasia are characterized by a pleomorphic population of lymphocytes, histiocytes, polymorphonuclear leukocytes, plasma cells, and other lymphoid elements. The smears showing non-Hodgkin's lymphoma are characterized by a monomorphic population of abnormal lymphoid cells; we have further classified these cases as diffuse large cell, large cell immunoblastic, and small noncleaved lymphomas. The smears of patients with mycobacterial infections have consisted of histiocytes with thousands of intracytoplasmic organisms. The smears showing Kaposi's sarcoma have clusters of bland spindle cells not associated with inflammatory elements.

Falsely abnormal results ("false-positives") of FNA biopsies of lymph nodes in this group of patients did not occur in our series, but falsely normal ("false-negatives") results can occur. Possible reasons for false-negative results include sampling errors in lymph nodes with focal disease, taking a biopsy of a benign lymph node in a patient with abnormal nodes elsewhere, and error in microscopic interpretation. Because false-negative FNA biopsies can occur, it is imperative that clinicians using this test realize that a benign result does not entirely rule out involvement of the lymph node by a malignant or infectious process.

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DNA Fingerprinting—Applications for Resolving Medical, Legal, and Criminal Issues

THERE IS NOW a genetic test to determine individual identity. This DNA test or "DNA fingerprinting" holds the same standard of certainty as a set of fingerprints. The test exploits the occurrence of tandem-repetitive regions of DNA—minisatellites—which are scattered throughout the human genome. The minisatellites are highly polymorphic or hypervariable, resulting from unequal exchanges that vary the number of short repeat units in a minisatellite. Researchers at Leicester University, England, isolated three human minisatellite DNA fragments by molecular cloning, each containing tandem repeats of closely related variants of a short consensus sequence. Using these cloned DNA fragments as probes to detect the homologous sequences in the restriction endonuclease-digested human DNA, they discovered DNA banding patterns ("fingerprints") that are completely specific to each person. The estimated frequency of unrelated persons showing the same DNA fingerprint is extremely low—5×10^{-19}—and for siblings to share the same pattern is only 1×10^{-6}.

The possible applications of this test to various fields are immense. It opens up a novel approach in forensic science: bits of tissue, stains of blood, or other body fluids left at the scene of a crime may be used to identify their human source. The test has already been done by the Leicestershire police to identify a murderer in a group of several thousand suspects. A miniscule specimen is sufficient to yield a few micrograms of DNA, material whose stability confers an additional advantage for its use as a marker for identification. The state of California is planning a computerized data bank of DNA fingerprinting information on convicted criminals to facilitate the rapid identification of repeat offenders. The test is also conclusive for all practical purposes in resolving cases of controversial parenthood or other familial relationships. Recently, an immigration case concerning questionable maternity was settled by DNA fingerprinting, permitting the son's emigration to England. Routine DNA fingerprinting by immigration authorities should accelerate the application process and avoid cases of arbitrary judgment by immigration officials.

The test provides an unequivocal criterion for discriminating between monozygotic and dizygotic twins of the same sex at birth, until now a problematic area in genetic studies involving human twins. Other potential medical applications of the test include monitoring engraftment of donor marrow;

ascertaining the source of clinical specimens in cases of mix-up; and, perhaps eventually, with an expanded range of minisatellite probes or appropriately synthesized oligonucleotide probes, examining genetic predispositions for diseases for which suitable markers are lacking.

With dramatic success already shown, there is a growing commercial interest in the test, and, in fact, the Imperial Chemical Industry has opened in the United Kingdom its first laboratory for DNA fingerprinting.

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Lymphocyte Gene Rearrangement Studies in Formalin-Fixed, Paraffin-Embedded Pathology Specimens

THE USE OF RECOMBINANT DNA TECHNOLOGIES to detect clonal rearrangements of immunoglobulin or T-cell receptor genes is becoming an increasingly valuable adjunct to more conventional methods in the diagnosis and assessment of B- or T-cell lymphoproliferative disorders. Until recently this technique depended on the availability of fresh or frozen tissue specimens, limiting its applicability in clinical medicine. We have therefore examined the feasibility of using our previously reported procedure for extracting DNA from formalin-fixed pathology specimens for gene rearrangement studies in such specimens.

We were able to show clonal rearrangement of heavy and light chain immunoglobulin genes in about 75% of blocks of formalin-fixed, paraffin-embedded B-cell lymphoma specimens retrieved from the pathology archives at our institution. The success rate at recovering intact high-molecular-weight DNA varied substantially depending on the hospital center from which the paraffin blocks were obtained. The most common reason for failing to recover high-molecular-weight DNA was the use of suboptimally fixed tissue containing partially autolysed areas. Overfixed material was also unsuitable because the amount of intact DNA recovered decreased with the increasing time of exposure to fixative. Tissues immersed in mercuric chloride-containing fixatives such as Zenker's or B5 were not suitable for gene rearrangement studies.

The best results will, therefore, be obtained with tissues sectioned and fixed in buffered formalin immediately after the surgical procedure and preferably for a period of no longer than 24 hours before being embedded in paraffin. Tissues fixed for as long as five days may still be usable, but the quantities of material recovered would be much smaller. Despite its limitations, this technique increases considerably the number of specimens amenable for gene rearrangement studies and should make this approach more applicable to the clinical evaluation of lymphoproliferative disorders.

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Neuropathology of AIDS Dementia

THE AIDS DEMENTIA COMPLEX (ADC) was recognized two to three years ago as a syndrome of progressive neurologic dysfunction that occurs in a substantial proportion of patients with the acquired immunodeficiency syndrome (AIDS). Patients with AIDS may have neurologic abnormalities as a result of one or more of several types of neuropathologic disorders, including opportunistic infections caused by viruses—such as cytomegalovirus, papovavirus, Herpes simplex and zoster viruses—*Toxoplasma gondii,* and fungi such as *Cryptococcus neoformans,* lymphoproliferative disorders including lymphoma and lymphomatoid granulomatosis, and vascular or anoxic-ischemic lesions. Peripheral neuropathy is also frequently found. Early in the AIDS epidemic, however, it became clear that cerebral dysfunction developed in some patients in the absence of any of these specific causal factors. Instead, postmortem examination of the patients' brains revealed poorly defined inflammatory lesions including scattered microglial nodules and perivascular lymphocytes, and myelin loss with intense astrogliosis within white matter of the centrum semiovale of the cerebral hemispheres. Furthermore, Southern blotting methods, in situ hybridization, immunocytochemistry, and electron microscopy showed the presence of the human immunodeficiency virus (HIV) in the brains of many of these patients. A small but definite subset of patients seropositive for HIV appeared to have "pure" brain involvement by this disease without peripheral or systemic manifestations of the syndrome, apparently reflecting neurotropism of HIV in these patients.

Though the ADC is now a recognized and reasonably defined clinicopathologic disorder, its nosology is by no means clear. Patients with the ADC often appear demented out of proportion to the amount of structural damage in the nervous system, although the observed dementia corresponds to the subcortical type expected in patients with primarily white matter brain damage. Conversely, evidence of HIV infection of brain is seen in neurologically normal patients. Although HIV forms with tropism for the nervous system have emerged, the cell type in the brain most commonly infected by HIV is one with macrophage or microglial markers. Infection of astrocytes has been recorded in a few cases, and there is little evidence for infection of neurons or oligodendrocytes. One hypothesis is that HIV-infected macrophages release a product or toxin that damages adjacent white matter.

The pathologic diagnosis of ADC due to HIV infection of brain is based on fairly subtle criteria. White matter injury may be inconspicuous unless large myelin-stained sections are carefully examined. Astrogliosis is best determined using an immunocytochemical procedure for glial fibrillary acidic protein. Finally, perivascular multinucleated cells—including giant cells—with foamy or granular cytoplasm are generally accepted as a marker for HIV within the nervous system. Commercially available antibodies and probes for HIV can also be used for immunocytochemistry or in situ hybridization. The diagnosis can even be made on brain biopsy, but this must be done with great caution because similar, though not identical, white matter changes without the